# OZENA AND ITS RELATION TO TUBERCULOSIS.

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Although not an uncommon disease, ozena has been relegated so strictly to the sphere of the rhinologist and the laryngologist that it is but little known outside these specialties. For a great many years there have been scattered references in the literature pointing out the frequency with which ozena and tuberculosis are to be observed in the same patient. This fact has been recognized in a general way, but has by no means been accorded the attention it deserves. Recent work done along these lines emphasizes the necessity of a more general knowledge of the symptomatology and therapy of ozena on the part of the medical profession as a whole. The frequent incidence of tuberculosis in ozenatous patients makes it of as much importance for the internist to recognize and examine a case of ozena as a possible subject of pulmonary involvement as it is for the nose and throat specialist to be familar with the various systemic diseases, of which derangements in his own particular field of observation are only part and parcel.

It will be the object of the following paragraphs to set forth the evidence at hand concerning the coincidence of these two diseases, together with the results of some experimental work done on the subject in the department of laryngology of the Johns Hopkins Hospital.

The word "ozena" is derived from the Greek, and means literally a stench. The lesions are confined to the mucous membranes of the nose, pharynx and may extend to the larynx. It is characterized by the formation of greenish-black crusts, with a sickening odor. It usually begins in childhood and runs a progressive course, tending to become less severe as old age advances. A predilection for filth makes it more common among the lower classes. Children of ozenatous parents are often found to be suffering with the same malady, and there is considerable evidence to show that it is contagious. The appearance of a well-developed case is often one of marked cachexia and malnutrition.

In the first stages there is a transient hypertrophy of the turbinates. Eventually the mucous membrane lining of the whole nose undergoes atrophy and all lymphoid and secretory structure disappear completely. Ulceration is not the rule. An idea of the profound changes that take place in the histological picture may be gained from the accompanying photomicrographs. Fig. 1 shows a section through the mucous membrane of a comparatively normal

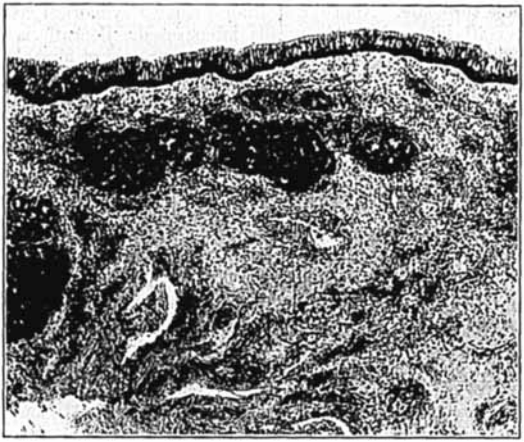

FIG. 1.—Section through the mucous membrane of a comparatively normal middle turbinate, showing columnar epithelium and glandular structures.

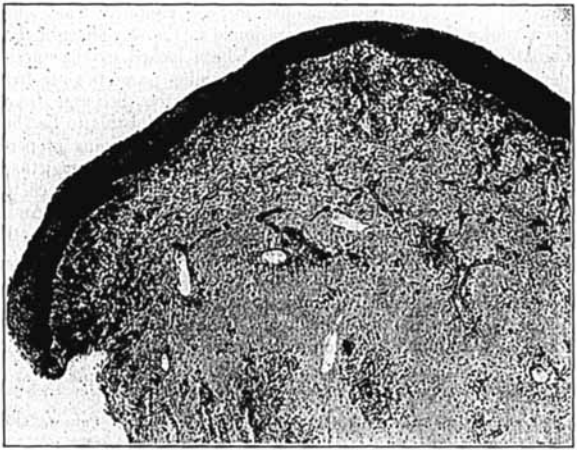

FIG. 2.—Section through the mucous membrane of the middle turbinate taken from a case of ozena, showing the stratified epithelium and entire absence of glandular structure. There is no evidence of tubercle.

middle turbinate. Note the stratiform ciliated cylindrical columnar epithelium with goblet cells interspersed. Beneath is the basement membrane and finally the tunica propria of fibro-elastic tissue with its venous plexuses and tubo-alveolar glands. Contrast this with Fig. 2. One can scarcely realize they are from the same anatomical locality. The stratiform columnar epithelium has been entirely replaced by a layer of stratified epithelium desquamating on the surface. Polymorphonuclears and small round cells are fairly abundant in this layer and in the one immediately below it, which corresponds to the submucosa. In the deeper structures, plasma cells, fibroblasts and eosinophils are found. There are numerous bloodvessels and venous plexuses. The striking feature is the complete absence of all glandular and secretory structure so abundant in the normal nose. Note will also be made of the complete absence of any structure resembling tubercle.

Many organisms have been mentioned in connection with the etiology of ozena. Among the better known are (1) the Abel-Löwenberg[1] bacillus, described by Abel in 1893, and (2) the cocco-bacillus fetidus ozenæ discovered by Perez,[2] and with which he claimed to have reproduced in rabbits lesions characteristic of ozena. The third organism identified with the disease is an acid-fast bacillus, and it is concerning the significance of this organism in the nasal secretions of ozena that a great deal of the controversy of recent years has had to do. Although it has long been known that such bacteria are found in the secretions of the ozenatous nose, they have in general been looked upon as accidental, just as similar flora with acid-staining properties are frequently present in sebaceous secretions, in the discharge from chronic ears, etc. Not everyone, however, admits this to be the case. There are those who hold that the acid-retaining properties of this particular bacillus have a more sinister meaning; that if it is not the tubercle bacillus it bears such a resemblance to that organism as to demand more than a casual notice. And, indeed, there is considerable ground for their contention, both clinically and bacteriologically.

As early as 1882 Fränkel[3] collected from the literature records of 6 cases of ozena which had come to section. Five of these were found to have definite tuberculosis. In Alexander's[4] series of 22 cases 15 were found to have died of tuberculosis. On the clinical side there is even more significant evidence. Alexander in the paper quoted above found a family history of tuberculosis in 16 of 22 cases. Wingrave[5] found a similar history in 37 out of 60 cases. Caboche[6] found a family history of phthisis in 16 of his 39 cases. In our own series 4 of the 8 cases in which a family history was obtained were found to have tuberculous antecedents.

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[1] Bakteriologische Studien über Ozaena Simplex, Centralblatt für Bakteriologie, 1893, xiii, p. 161.

[2] Recherches sur la bacteriologie de l'ozena, Annals de l'Institut Pasteur, 1899, xiii, p. 937.

[3] Pathologische Mittheilungen, ii Beiträge zur Rhinopathologie, Virchows Arch., 1882, lxxxvii, p. 285.

[4] Die Bezeihungen der Ozaena zur Lungentuberculose nebst Bemerkungen über die Diagnose der Ozaena, Arch. f. Laryngol. u. Rhinol., 1903, xiv, p. 1.

The incidence of tuberculosis in people suffering with ozena is just as striking. Alexander in the same monograph records 50 cases of ozena in which definite pulmonary tuberculosis was found in 22, suspicious tuberculosis in 7 and pulmonary lesions of a different character in 4. Theisen[7] found phthisis in 7 out of 20 cases of ozena. McKenzie[8] in 34 cases found 5 with pulmonary tuberculosis and 3 with other tuberculous manifestations. Mackeith[9] found "phthisis pulmonalis" in 4 out of 13 cases. In our own series of 9 cases 3 showed frank pulmonary tuberculosis and 3 evidence of less active lesions. In other words, 40.4 per cent. of the cases cited above showed a more or less definite clinical tuberculosis and 56.6 per cent. gave a family history of phthisis.

These figures would certainly indicate something more than a mere accidental association of the two diseases. What then is this relationship? Before attempting an answer let us return to a consideration of the acid-fast organisms found in the crusts in ozena.

The tinctorial qualities of these bacilli can be demonstrated in almost all true cases of ozena. We have not found them in other diseases simulating ozena, such as syphilis of the nose. When found they are most abundant in the thick black crusts of a fully developed case. The best preparations are obtained by taking a bit of the crust, dissolving it in sterile salt solution and spreading it on a slide with a platinum loop. Fix by passing several times through a flame. Overheating will cause the organisms to swell and become distorted. Stain in the usual manner by the Ziehl-Neelsen method.

Owing to the fact that many of these bacilli are not alcohol-fast, it is best to decolorize only in an acid bath, using 25 per cent. sulphuric acid. The preparation is counterstained with methylene blue. The acid-fasts will be found to stand forth a bright red in contrast to the blue of the other organisms. They vary greatly in their morphology, ranging all the way from streptothrix-like clumps to short, thick rods. They frequently occur as thin, curved, beaded rods, identical in appearance with the tubercle bacillus.

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[5] Atrophic Rhinitis, Journal of Laryngology, Rhinology and Otology, 1894.

[6] L'ozène forme larvée de la tuberculose, Ann. d. mal. d. l'orielle, du larynx (etc.), 1917, xxxiii, pt. ii, p. 260.

[7] Etiology and Diagnosis of Ozena and its Relation to Pulmonary Tuberculosis, Albany Medical Annals, 1904, xxv, p. 140.

[8] Atrophic Rhinitis (Ozaena) and Tuberculosis, Journal of Laryngology, Rhinology and Otology, 1910, xxxi, p. 176.

[9] Atrophic Rhinitis (Ozaena) and Tuberculosis, Pt. ii, Tuberculin in Atrophic Rhinitis, Journal of Laryngology, Rhinology and Otology, 1916, xxxi, p. 232.

With the assistance of Dr. Esau Greenspon, of the pathological department, an attempt was made early in the year 1918 to cultivate these organisms. Crusts were washed several times in sterile saline solution and implanted on Dorset egg medium, sheep serum agar, blood agar and other media. Unfortunately for our work Dr. Greenspon was called to the colors at this time, and this fact, coupled with other exigencies brought on by the war, forced us to abandon this phase of the work. However, the organisms in question have been isolated and grown by Wingrave,[10] using Dorset egg medium reinforced with ozena crusts.

**Animal Experiments.** In the paper last quoted there is, furthermore, recorded an account of guinea-pig inoculations. Six animals were injected, using a reinforced emulsion made from ozena crusts. At section the 3 animals which had been injected intraperitoneally were found to have escaped all infection. The 3 which had been inoculated subcutaneously showed definite tuberculosis, with caseation of glands, giant-cell formation and "tubercle bacilli in and around the giant cells."

Our experiments along these lines have not been so successful. Crusts were collected from 5 cases of ozena in which we had first demonstrated the presence of acid-fast bacilli. An emulsion of the crusts was made from each case and 3 c.c. of this injected into guinea-pigs, using 2 animals to each patient. The intraperitoneal method was used. At the end of four weeks several animals had died of intercurrent infections—no gross signs of tubercle were found at autopsy. Smears and sections from various organs were stained with similar results. The remaining animals were sacrificed at the end of six weeks. No signs of tuberculosis were found. A second group was inoculated, with the same disappointing results. Recently a third series of animals was injected, using material from one new and two old cases. This time the emulsion was introduced subcutaneously. The regional lymph glands became swollen within a week. The animals died during the fourth and fifth weeks. They were carefully examined, but no histological evidence of tubercle was found in the glands or viscera.

As before mentioned we first ascertained the presence of the acid-fast organisms in the material used. Arguing from the well-known susceptibility of the guinea-pig to the tubercle bacillus we are forced to conclude, from our experiments, that the acid-fast bacillus found in the nasal secretions of ozena is not identical with the tubercle bacillus.

**Tuberculin Therapy.**—It would entail too much space to go into the many methods advocated in the treatment of ozena. Their very number and diversity are an indication of our lack of true information on the subject. In general there are two classes of therapy employed. Local measures in the form of irrigations, suppositories, instillations and paraffin injections. In the second group fall the various forms of vaccinotherapy. The first class of remedial agents acts apparently in a purely mechanical manner and are efficacious only so long as one persists in their use.

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[10] Atrophic Rhinitis (Ozaena) and Tuberculosis, Pt. iii, The pathological Aspect, Journal of Laryngology, Rhinology and Otology, 1916, xxxi, p. 276.

Results of a more lasting character are claimed from the use of vaccines. Hofer and Kofler,[11] using a vaccine made from the Perez bacillus, reported favorable results. Subsequent reports on the use of this vaccine conflict. Golgau[12] experimented with seven different varieties of vaccines, and from his results concludes that all such forms of therapy are of little or no value. Mackeith,[13] starting with the premise that ozena is a tuberculous manifestation, has treated a series of 13 cases with tuberculin. His results have been very good. Some of these patients have been under observation as long as two and a half years after treatment was inaugurated. Of these 7 showed great improvement, 3 improvement, 2 suffered relapse and 1 case was not benefited.

In January, 1918, we mailed cards to about 100 names indexed in the nose and throat dispensary under the headings "Ozena" and "Atrophic Rhinitis." Of this number about 40 reported for examination. Our task was to pick out only those which we considered to be genuine cases of ozena. We chose as our more important criteria the characteristic fetor, atrophy of the mucous membranes and the presence of the greenish-black crusts in the nose. When possible smears were made to determine the presence of acid-fast bacilli. From this group we have been able to obtain fairly complete records of 9 cases of what we consider to be true ozena. As the patients reported they were given the routine nose and throat examination, including roentgen ray of the sinuses and Wassermann test. Of the 9 cases, 7 consented to undertake the tuberculin treatment, for the administration of which as well as for the chest examinations we are indebted to the Phipps Tuberculosis Dispensary.

The tuberculin used was the human bouillon filtrate. An initial dose of from $\frac{1}{1000000}$ to $\frac{3}{1000000}$ mg. was given and the dosage increased gradually until at the end of a year the patient received 1000 mg. each month. A glance at the following abstracts will give an idea of the success that has attended our treatment of ozena with tuberculin:[14]

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[11] Bisherige Ergebnisse einer neuen Vakzinationstherapie bei Ozena (Cocco bacillus fetidus ozena Perez), 1913, xxvi, No. 42, p. 1698.

[12] Vaccine Treatment of Ozena, Laryngoscope, 1918, xxviii, p. 380.

[13] Loc. cit.

[14] These observations were carried up to September, 1920.

CASE I.—H. K., male, white. Birthplace, United States. Laborer. Aged twenty-nine years. Complaint: "Pimple in the nose." Admitted January 3, 1918.

*Family History.* Negative.

*Past History.* Negative, except for chronic nasal discharge.

*Personal Examination. Temperature,* 99.2°. *Roentgen-ray sinuses,* negative. *Wassermann,* negative. *Glands,* not enlarged. *Nose,* inferior turbinates atrophied; both sides filled with foul-smelling discharge and greenish crusts. *Smear* from nose showed numerous acid-fast bacilli. *Chest Examination:* slight impairment to the third rib on the right and left and throughout the back. Breath sounds diminished. *Von Pirquet test* slightly positive. *Roentgen ray of chest:* spotty infiltration of both lungs, especially on the right side, tuberculous in origin. *Diagnosis:* possibly some fibrosis of both uppers.

*Course.* At the end of three months, during which time he was seen weekly, this patient showed a marked improvement. The discharge disappeared almost entirely and lost its disagreeable odor. His general health became better, with improvement in appetite and a gain of ten pounds in weight. From this time to the present his condition has remained about stationary. He now receives the maximum dose of 1000 mg. each month. He has discontinued all irrigations and other treatment.

CASE II.—A. L., male, white. Birthplace, United States. Schoolboy. Aged thirteen years. Patient referred for consultation from the Phipps Tuberculosis Dispensary December 27, 1917.

*Family History.* Mother has tuberculosis. One sister died of tuberculosis.

*Personal History.* Scarlet fever and diphtheria in infancy. Profuse discharge in nose for some time.

*Personal Examination. Temperature,* 99.2°. *Wassermann,* negative. *Glands,* not enlarged. *Nose,* middle turbinates atrophied; dry, foul-smelling discharge throughout the nose. *Tonsils,* not enlarged. *Chest Examination:* manubrial dulness; impairment to second rib and to the lower angle of the scapula behind. *Impression,* mediastinitis. *Von Pirquet,* positive. *Roentgen ray chest,* marked fibroid infiltration of the right lung; probable thickening of the pleura. *Diagnosis:* changes probably tuberculous in origin.

*Course.* Patient has been under tuberculin treatment for a year. The odor has disappeared and the discharge has practically ceased. He has gained in weight. At present is receiving 1000 mg. of tuberculin each month.

CASE III.—M. F., female, negress. Birthplace, United States. Aged eighteen years. *Complaint,* nasal discharge.

*Family History.* None obtainable.

*Personal History.* Nasal trouble for past year.

*Personal Examination. Wassermann,* negative. *Roentgen-ray sinuses,* clouding both antra. *Glands,* not enlarged. *Nose,* inferior turbinates atrophied; thick, greenish crusts with typical fetor. *Tonsils,* atrophic. *Nasopharynx,* walls covered with greenish crusts. *Smear* from the nose showed acid-fast bacilli in large numbers. *Chest Examination:* possible minimal left apical tuberculosis; rales heard.

*Course.* After an irregular course of treatment for three months the patient returned and volunteered the information that her subjective symptoms had disappeared. Examination of the nose showed practically no discharge and no odor. The patient could not be prevailed upon to continue treatment.

CASE IV.—M. V., female, white. Birthplace, United States. Schoolgirl. Aged fourteen years. *Complaint,* sunken nose. Admitted June 25, 1919.

*Family History.* One sister has nose trouble (ozena).

*Personal History.* Nose has been "sinking for several years;" offensive discharge; complete anosmia.

*Personal Examination. Temperature,* 98.8°. *Wassermann,* negative. *Roentgen-ray sinuses,* infection of right frontal, ethmoids and antrum. *Glands,* just palpable in anterior and posterior triangles. *Nose,* external deformity; interior filled with thick, black crusts with a disagreeable odor; atrophy of both inferior turbinates; antra irrigated and fluid returned clear. *Smear* from nose showed numerous acid-fast bacilli. *Chest examination,* negative. *Von Pirquet,* slightly positive.

*Course.* There was an apparent flare-up of the nasal condition and some local reaction after the first seven injections of tuberculin. At the end of six months the discharge had practically disappeared together with the odor.

About one year from the time the treatment was commenced the patient suffered a relapse, with a return of the discharge and odor. She is still under treatment.

CASE V.—C. G., female. Birthplace, United States. Occupation, housework. Aged twenty-three years. *Complaint,* trouble with nose and throat. Admitted March 5, 1918.

*Family History.* Negative.

*Personal History.* Occasional headache. Post-nasal discharge for two years.

*Personal Examination. Temperature,* 97.8°. *Wassermann,* negative. *Roentgen-ray sinuses,* negative. *Glands* are just palpable in the posterior triangles of the neck and at the angles of the jaw.

*Nose,* atrophy of both inferior turbinates; profuse purulent discharge on both sides, with odor. *Tonsils,* atrophic. *Chest Examination,* negative for tuberculosis.

*Course.* After five months' treatment with tuberculin the patient reports that she thinks the discharge is considerably less. Examination shows a slight amount of discharge on the left side. *It is worthy of note that nine months after first being seen this patient developed pulmonary tuberculosis while under observation.*

CASE VI.—M. C., female. Birthplace, United States. Schoolgirl. Aged ten years. *Complaint,* nasal odor and nasal discharge. Admitted October 25, 1919.

*Family History.* Mother has pulmonary tuberculosis.

*Personal Examination. Wassermann,* negative. *Roentgen-ray sinuses,* negative. *Glands,* not enlarged. *Nose,* foul, greenish crusts in the posterior nares and in the nasopharynx. All turbinates atrophied. *Smear* showed numerous acid-fasts. *Chest examination,* negative. *Von Pirquet,* negative.

*Course.* After five months' treatment with tuberculin, the nose shows only a small amount of discharge on the right side. Odor not marked. From this time until the present date the patient has suffered several remissions. At no time, however, has her condition been as bad as when first seen.

CASE VII.—J. R., male. Birthplace, United States. Clerk. Aged twenty-eight years. *Complaint,* atrophic rhinitis.

*Family History.* Mother died of pulmonary tuberculosis.

*Personal History.* Had attacks of chills and fever for eight years. Cough and pain in chest. Formation of foul-smelling crusts in the nose since childhood. Anosmia.

*Personal Examination. Glands* are just palpable at the angles of the jaws. *Nose,* septum deflected to the right; left side filled with typical foul-smelling discharge. *Pharynx,* purulent discharge on the posterior wall. *Sinuses* are clear. *Smear* from nose showed acid-fast bacilli in large numbers. *Chest examination,* breath sounds and percussion note impaired at both apices. (Examination made outside the hospital.)

*Course.* After three months' treatment with tuberculin the patient reported for examination. He says that those with whom he is in daily contact no longer complain of the odor. Examination of the nose showed about half the amount of discharge first noted.

CASE VIII.—F. K., white. Birthplace, Bohemia. Occupation, farmer. Aged forty-seven years. *Complaint,* throat trouble. Admitted November 6, 1918.

*Family History.* Negative.

*Personal History.* Cough for one year.

*Personal Examination. Glands* not palpable. *Nose,* turbinates atrophied; discharge, with fetid odor.

*Chest Examination.* Impairment of the upper right and left; rales on the left side. *Tubercle bacilli* present in the sputum. *Roentgen ray chest,* spotty infiltration of left upper and right apex. *Diagnosis,* pulmonary tuberculosis. In this patient the onset of tuberculosis and ozena were apparently simultaneous.

*Course.* Not treated for nasal condition.

CASE IX.—E. S., male, white. Birthplace, United States. Aged sixty-nine years. *Complaint,* catarrh and deafness. Admitted May 10, 1920.

*Family History.* Probable history of tuberculosis and ozena in family.

*Personal History.* Nasal discharge since early adult life.

*Personal Examination. Temperature,* 98.4°. *Wassermann,* negative. *Roentgen-ray sinuses,* clouding of left frontal and ethmoids. *Glands,* not enlarged. *Nose,* inferior turbinates atrophied; middle turbinates, covered with thick, greenish crusts, with foul odor. *Nasopharynx* shows same picture as nose.

*Chest Examination.* Fibroid changes over uppers; marked on right side; few persistent râles above right clavicle. *Roentgen ray,* old fibroid tuberculosis of left upper.

*Course.* Not treated.

To summarize:

Cases I and II show great improvement two and a half years after treatment was started.

Cases III and VII show improvement after three months' treatment.

Case V showed an initial improvement after five months' treatment. Four months after stopping treatment she developed pulmonary tuberculosis.

Cases IV and VI showed an initial improvement followed by relapse—No. IV after one year's treatment and No. VI after five months' treatment.

By improvement we mean cessation of discharge and a better condition of health in general. In none of the cases was the atrophy in the nose affected. In some the sense of smell returned to a certain extent.

The good results reported from the use of other vaccines make us wary of attributing to the tuberculin any specific action on the nasal condition. At any rate whether the amelioration of symptoms following the use of tuberculin be due to a general tonic action or is the result of the introduction of a foreign protein into the blood or whether there is some direct action on the nasal disease is beside the question. The fact remains that of the various remedies we have heretofore tried in the treatment of ozena by far the best results have been obtained with the use of tuberculin.

Our results and those of Mackeith certainly warrant a more extensive trial of this form of therapy.

As intimated before, our main object has been to point out and insist upon the relation that exists between the disease ozena and tuberculosis.

We offer as evidence from our own and cases collected from the literature:

28 cases that have come to autopsy, tuberculosis was found in 20 and was the cause of death in 15 of these.

129 cases in which a family history of tuberculosis was demonstrated in 73.

126 cases in which definite clinical tuberculosis was found in 52.

It is true our laboratory tests argue against any etiological identity. On the other hand the clinical evidence cannot be dismissed as falling within the realm of coincidence. The question of the etiology of ozena has yet to be settled. That the disease is very frequently associated with tuberculosis is a fact—a fact that it behooves every practising physician to bear in mind and one that should cause him to investigate every case of ozena coming under his notice as a possible instance of tuberculosis.

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# DIABETES MELLITUS, SYPHILIS AND THE NEGRO.

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In view of Warthin's report that he has found syphilitic pancreatitis in all of the diabetic cases at the University of Michigan coming to autopsy, it has seemed worth while to examine from this point of view a material rich in syphilis. Warthin's[1] statement is "that diabetes may be associated with the more marked degrees of syphilitic pancreatitis, and in our autopsy series all of our diabetic cases have been so associated, but that a number of syphilitic pancreatitis of similar degree of severity have not presented the clinical symptoms of diabetes. It seems very probable, therefore, that latent syphilis is the chief factor in the forms of pancreatitis most frequently associated with diabetes, but that diabetes is not always associated with severe degrees of this type of pancreatitis." Since this report was made there has been very little discussion of the matter in the literature, though Warthin's contention has not gone altogether unchallenged. Thus, J. R. Williams[2] reported that only 4 out of 143 cases of diabetes mellitus gave a positive Wassermann and the

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[1] Am. Jour. Med. Sc., 1916, clii, 157.
[2] Jour. Am. Med. Assn., 1918, lxx, 365.